RATIONALE FOR THE TREATMENT OF LUPUS ERYTHEMATOSUS WITH ANTIMALARIALS*

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Although the dermal lesions of chronic discoid lupus erythematosus (1) were described more than a hundred years ago, many investigators feel that an ideal, specific diagnostic test is still lacking. Among the predisposing factors of this disease, photosensitivity seems to be of prime importance. Jessar and co-workers (2) claimed that sensitivity to sunlight was a precipitating factor in 272 of their cases, and Gold's observations (3) led him to the same conclusion.

Page (4) treated 18 cases, varying from chronic to acute discoid L.E. (in one case associated with rheumatoid arthritis), with mepacrine (quinacrine†), and noted improvement in 17 cases. In discussing the possible mode of action he pointed out that the drug reduced the dermal photosensitivity of his patients. He could, in fact, demonstrate a significant change in the reaction time to a minimal erythema dose between controls and patients who had received medication for ten days. Denzer and Blumenthal (5) have demonstrated that photosensitivity is a common symptom in discoid L.E., and that the toxicosis is a reaction of the ensuing peculiarly susceptible constitutional state.

It is interesting to speculate on the fact that the incidence of the disease is higher (88 per cent) in females (6, 7), since the lesions are confined almost entirely to those portions of the body which are not shielded by clothing. Familial tendencies are also noted (1). The so-called butterfly pattern of bilaterally symmetrical distribution, usually involving the face and occurring also on the arms and hands, which are typical sites for the eruptions, leads to the inescapable conclusion that the dermal manifestations of the disease are in some way associated with the effect of light on the exposed body surfaces.

It had been observed earlier that certain antimalarials such as quinacrine, (Atabrine®), which are intrinsically deeply colored, give visible evidence of deposition in the skin. This observation presumably led the Russian investigator Prokoptchouk (8) in 1940 to a trial of this drug in the treatment of 35 patients affected with discoid L.E. The following year another Russian clinician, Sorinson (9), undertook the treatment of L.E. in 70 patients, and noted favorable results after two courses of quinacrine. This management of the disease became well-known in several European countries, including Germany (10), Italy (11), and Great Britain (4). It was mainly the success which Page obtained in 17 of 18 patients (4) that caused clinicians in the United States to give serious thought to this type of chemotherapy. Encouraged by Page's report, O'Leary and collaborators (12) at the Mayo Clinic began the systemic treatment of L.E. with antimalarials in 1952.

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† Available from Winthrop Laboratories, under the trade-name of Atabrine.

The efficiency of quinacrine in the management of discoid L.E. has since been confirmed by many investigators. The reports of Rhodes and Allende (13), Somerville *et al* (14), Buchanan *et al* (15), and Michelson (16) may be regarded as typical. The success with quinacrine led naturally to the trial of other antimalarial drugs in the hope of avoiding the visible staining of the skin which is so characteristic of the former. Chloroquine* was found to possess the desired effect. Goldman *et al* (17) pointed out that it produced only an insignificant incidence of side effects, but stated that the response was slower than obtained with the acridine type of compound. Shee (18) successfully cleared up chronic discoid L.E. in patients who had been afflicted with the disease for as long as 14 years. Rogers and Finn (19) compared the two drugs and obtained satisfactory results with both. Similarly, Pillsbury and Jacobson (20), treated 16 chronic discoid L.E. patients with chloroquine and obtained good results.

Recently, Cornbleet (21) increased the armamentarium of antimalarials for the management of L.E. by reporting on another 4-aminoquinoline type drug, i.e. hydroxychloroquine.† All of his seven patients responded favorably to the therapy. Cornbleet's findings were confirmed on a larger series of patients by Lewis and Frumess (22). They were impressed with the rapidity of therapeutic response. Doses ranging from 600 to 2000 mg./day of hydroxychloroquine were administered to 40 patients by Mullins *et al* (23), who stressed the fact that larger doses of this drug seemed to be necessary, but also that patients who could not tolerate chloroquine could be managed successfully with the hydroxy analog. Like other authors, they postulated that the drug must be deposited in the skin, at the site of the lesions, in order to exert its activity.

In order to validate this sun-screening concept, one would need data on the skin distribution of the three antimalarials which have been discussed above. The fact that quinacrine localizes extensively in the skin is well-known, and qualitative statements to this effect have appeared many times in the literature (24 and 25). As regards quantitative data, Hecht (26) studied the distribution of quinacrine in the organs of mice, guinea pigs, cats, and rabbits. In mice which received 200 mg./kg. of the musonate (methane sulfonate) s.c. and were killed 48 hrs. later he found a concentration of 35 mg. per kg. of skin. In rabbits which received 15 mg. of the dihydrochloride per kg. i.m. and were killed 11 hrs. later he found 7.5 mg. per kg. of skin, while in rabbits which received 50 mg. of the dihydrochloride per kg. orally for 10 days and were killed 6 hrs. after the last dose he found 110 mg. per kg. of skin. The dosage schedules used in guinea pigs and cats did not result in extensive skin localization. Dearborn *et al* (27) administered quinacrine dihydrochloride in doses of 50 mg./kg./day orally to dogs for 14 days, and found skin concentrations ranging from 15 to 51 mg. per kg. of skin on the 14th day. After giving 5 mg. of quinacrine dihydrochloride per kg. per day for 78 days, they found skin concentrations of 4–5 mg./kg. Barlow, Auerbach and Rivenburg (28) noted obvious concentrations of quinacrine in the skin of rats medicated repeatedly with the drug, but did not determine the exact amounts

* Available from Winthrop Laboratories, under the trade-name of Aralen.

† Available from Winthrop Laboratories, under the trade-name of Plaquenil.

present. The Army Malaria Research Unit at Oxford University noted (29) the presence of quinacrine in the hair and perspiration of dogs and rats medicated with the drug, but did not determine skin concentrations. Concentrations of quinacrine in the skin of man, following its oral administration, have been recorded by Lange and Matzner (30) in arbitrary units.

There are several reports in the literature on the distribution of chloroquine in the tissues of such species as dog, monkey, and rat (31, 32). Its widespread distribution would imply its presence in skin, but this tissue was not included among those studied. Data on chloroquine and hydroxychloroquine (33) indicate that their tissue distribution is quite similar; the species studied were dogs and rats. However, again, skin had not been included in the tissues studied; therefore it was necessary to obtain this information. Quinacrine was included in the experiment so that strictly comparable data would be available.

EXPERIMENTAL

Male white rats weighing 140–160 gm. were medicated according to two dosage schemes: group A received orally 5 mg./kg. of the drug (calculated as base, but given as the diphosphate salt of chloroquine and hydroxychloroquine, and as the dihydrochloride of quinacrine) at zero hrs., followed by 2.5 mg./kg. at 8 hrs. and 2.5 mg./kg. at 24 hrs. Group B received 15 mg./kg. of the drug at zero hrs., followed by the same dose at 8 and 24 hrs. The total dose for group A, therefore, was 10 mg. base/kg., and for group B, 45 mg. base/kg. The animals were killed 2 hrs. after the last dose, and analyses of liver and skin were made. The skin was prepared by removing most of the hair with an electric clipper, and then shaving as cleanly as possible. Both tissues were homogenized in water, the extracts were made alkaline, shaken with ethylene dichloride, and the drug concentrations were determined as follows: quinacrine by the method of Brodie and Udenfriend

TABLE I

*Skin and liver concentrations (as mg. base/kg. wet weight) of some antimalarials in rats following the oral administration of 3 doses in 24 hrs.**

Chloroquine		Hydroxychloroquine		Quinacrine	
Skin	Liver	Skin	Liver	Skin	Liver
A. Total dose = 10 mg. base/kg.					
1.6 ± 0.19†	9.5 ± 0.62	2.5 ± 0.28	11.0 ± 0.36	4.0 ± 0.43	31.7 ± 2.7
Ratio, skin/liver 0.17		0.23		0.13	
B. Total dose = 45 mg. base/kg.					
11.5 ± 1.8	63 ± 3.0	5.9 ± 0.31	39.3 ± 8.7	15.3 ± 1.3	140 ± 11
Ratio, skin/liver 0.18		0.15		0.11	

* Animals killed at the 26th hour.

† Concentrations are recorded as mean ±s.e. There were 6 animals per group.

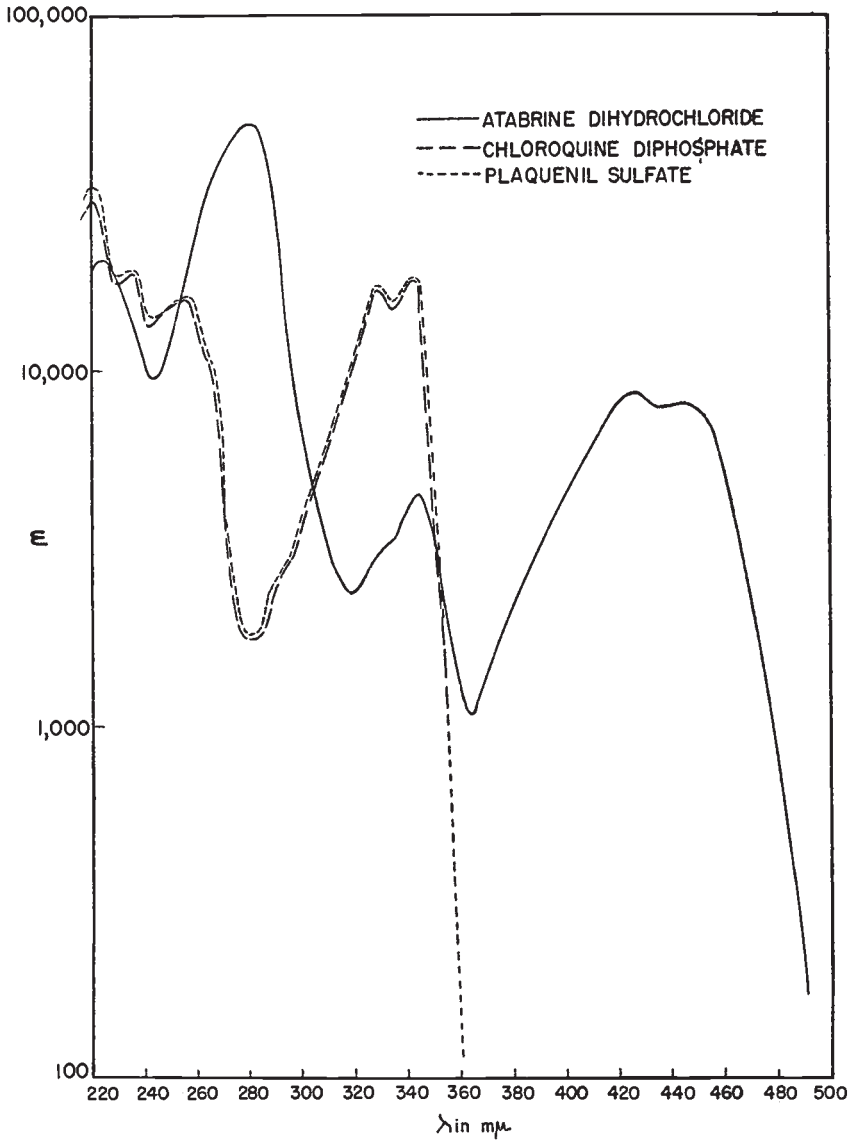

FIG. 1. Ultraviolet absorption spectra of quinacrine, chloroquine and hydroxychloroquine salts in water.

(34); chloroquine and hydroxychloroquine by the procedure of McChesney, Wyzan and McAuliff (35). The results are presented in Table I.

Comments: At the lower dose level (A) the tissue concentrations of chloroquine are less than those of hydroxychloroquine or quinacrine. The higher skin concentration of quinacrine, as compared to hydroxychloroquine, is accompanied by a much higher hepatic concentration, with the result that the skin/liver ratio is greatest for hydroxychloroquine. The marked tendency of quinacrine to localize

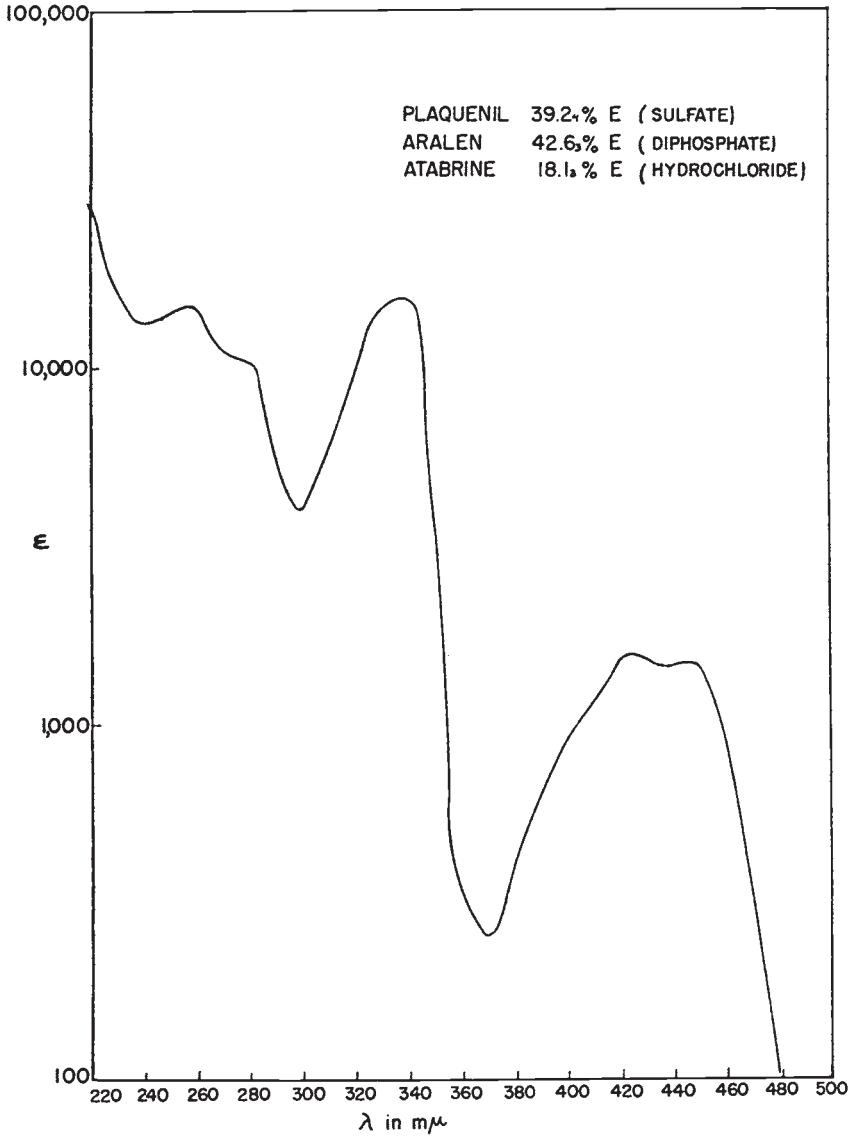

FIG. 2. Ultraviolet absorption spectrum of a (ca.) 2:2:1 molar ratio of chloroquine, hydroxychloroquine and quinacrine salts in water.

in liver is well-known (26–29). The higher dose level (B) produces increases in quinacrine concentrations in both skin and liver almost exactly proportional to the increase in dose. However, the higher dose of chloroquine results in increases in both skin and liver concentrations which are considerably greater than the increase in dose. At this dose level it gives the highest skin/liver ratio. Hydroxychloroquine does not appear to be as rapidly absorbed as chloroquine on the higher dose.

At both dose levels, and with all three drugs, the skin concentrations are approximately 13 per cent of what would be found if the entire dose were absorbed and retained, with uniform distribution in all of the tissues. In one case (quinacrine, dose A), the fraction in skin is 20 per cent, on this same basis of reckoning. These concentrations are as high as one could expect considering the relatively poor circulation and low water content of the integument, and the fact that simultaneous degradation and excretion of the compounds tends to deplete the body stores.

Ultraviolet absorption: The UV absorption curves of the three antimalarials are shown in Fig. 1. The two 4-aminoquinolines have essentially identical spectra, owing to the identity of the aromatic portion of the molecules. Their maximum absorption extends beyond the 260mμ range, with a second doublet in the 330–350mμ region. On the other hand, the acridine molecule has a strong absorption band at 280mμ, where the absorption of quinolines is minimal. It also has maxima at $\approx$345mμ and in the visible range (400–460mμ), accounting for its yellow color.

Bearing in mind the higher distribution coefficient of quinacrine in the skin, it can be shown that a most effective actinic screen can be achieved by a combination therapy with a molar percentage of approximately 40:40:20, the quinacrine salt being represented by the last figure. The absorption spectrum of this combination of drugs in the actual mole fraction used is shown in Fig. 2. It can readily be seen that this combination affords a good "sun-screen", cutting out not only the erythemal but also the tanning rays of the sun's spectrum. We might add here that the metabolic products of the antimalarials, resulting from the deamination of the side chain would have equal absorptive power for ultraviolet light, since, as pointed out above, the absorption is connected with the electron density of the aromatic rings.

DISCUSSION AND SUMMARY

The present status of diagnosis and treatment of L.E. has been cogently summarized by Dubois (7). His statement reemphasizes the outstanding value of antimalarial therapy for this disease.

Support for the concept that the antimalarial drugs are effective in lupus erythematosus as a result of their sun-screening action has been provided here by the demonstration of their presence in skin, and of their property, particularly in suitable combination, of absorbing radiation in the region 220–360mμ. A formulation containing the three drugs thus has the advantage of absorption of radiation over a wide range of the spectrum, both visible and ultraviolet. Quinacrine absorbs well where the 4-amino-quinolines absorb rather poorly, and vice versa. The presence of both chloroquine and hydroxychloroquine in a formulation has an advantage, derived from the fact that these two compounds have somewhat different toxicity patterns in both a qualitative and a quantitative sense (36). This situation makes it possible to summate their sun-screening effects without increasing proportionately the toxicity which might be induced if either of these two antimalarials were given in double amounts.

Since the trigger of the L.E. syndrome is related to the Koebner phenomenon

(37), the dramatic success of treatment with antimalarials, and particularly with combinations of these drugs, is logically attributed to the screening out of harmful wavelengths, thereby preventing the photonic activation of the process.

Cahn *et al* (38) have shown that the action spectrum of erythema production in polymorphous light eruption does not coincide with the absorption spectrum of chloroquine, but Beal (39) has shown that the sensitivity spectrum of solar urticaria does coincide with the absorption spectrum of chloroquine. As far as is known to us, the specific sensitivity spectrum of lupus erythematosus, if it exists, has not been established. However, Cahn and co-workers indicate that the antimalarial in their studies "produces its effect by modifying the reaction pattern . . . in a manner which suppresses the abnormal but not the normal responses to ultraviolet light in the sunburn spectrum", which would agree quite well with the rationale here proposed.

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